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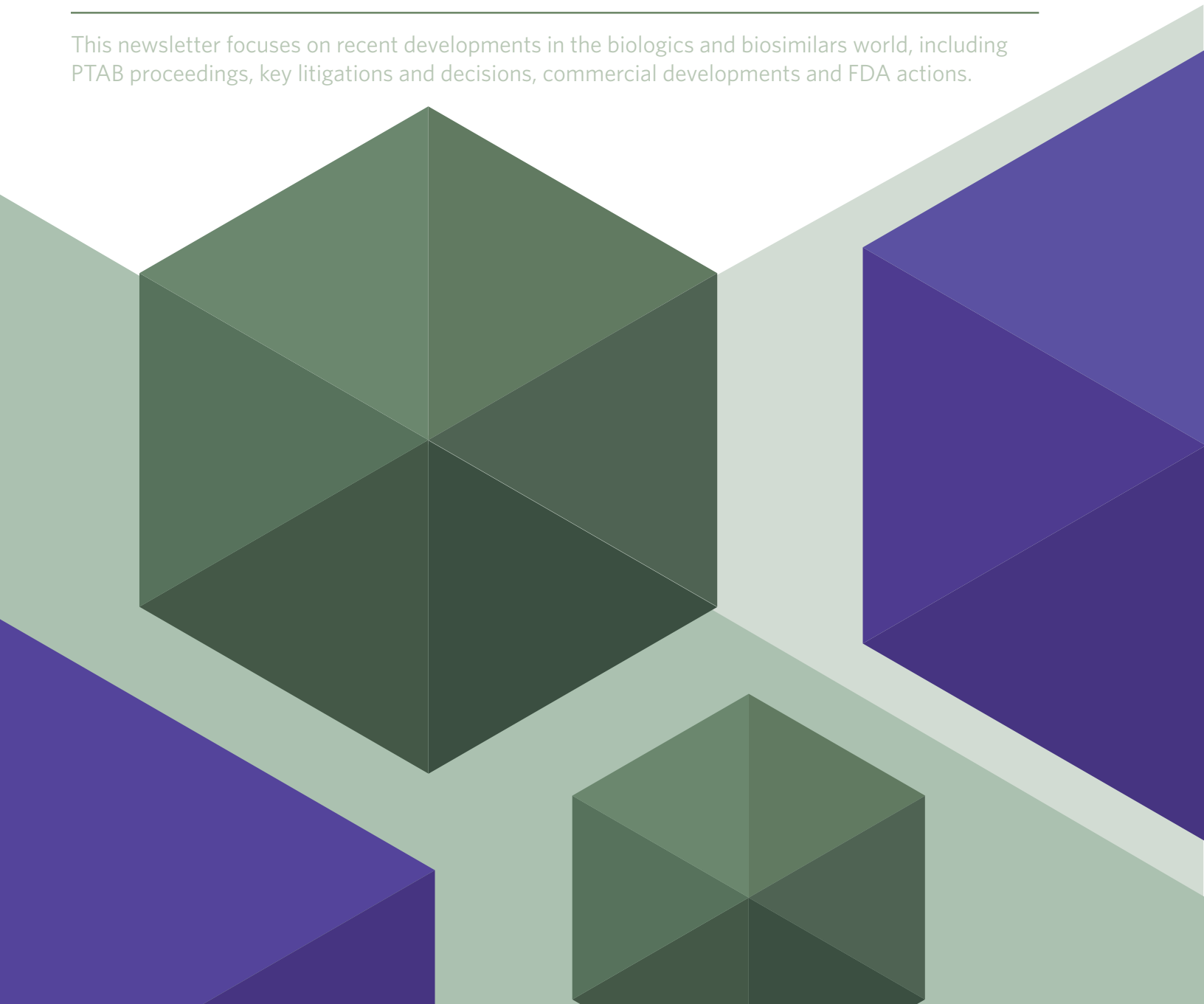
INTELLECTUAL PROPERTY NEWSLETTER

November 2020

THE BIO-QUARTERLY:
WILLKIE'S BIOLOGICS AND BIOSIMILARS NEWSLETTER

This newsletter focuses on recent developments in the biologics and biosimilars world, including PTAB proceedings, key litigations and decisions, commercial developments and FDA actions.



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Key developments at the Patent Trial and Appeal Board ("PTAB") regarding biologics

PTAB Quarterly Update

Insulin Glargine (Lantus®):

On June 6, 2020, the PTAB issued Final Written Decisions in IPRs filed by Mylan/Biocon and joined by Pfizer against Sanofi-Aventis for patents related to insulin, insulin analogs, and injectors for insulin. The Board found all challenged claims of U.S. Patent No. 8,603,044 unpatentable as obvious. The Board also found all challenged claims of U.S. Patent No. 8,992,486 unpatentable as obvious and denied Sanofi's contingent motion to amend. The Board found all challenged claims of U.S. Patent No. 9,526,844 unpatentable as obvious and denied Sanofi's contingent motion to amend.

For U.S. Patent No. 9,604,008, the Board found four challenged claims unpatentable and two challenged claims patentable. The Board found claim 3, which requires an insert that is secured in the housing against rotational and longitudinal motion, patentable because the prior art references did not include an insert secured against rotational motion and the Petitioner failed to adequately explain why a POSA would be motivated to combine references or have a reasonable expectation of success in combining references. The Board found claim 11, which requires a dose dial sleeve with a threaded outer surface engaged with an internal helical thread, patentable because the prior art references did not include a thread on the outer surface and Petitioner failed to adequately explain why a POSA would be motivated to combine references to use an external thread.

Eculizumab (Soliris®):

On June 1, 2020, three IPRs filed by Amgen against Alexion's patents directed to eculizumab and/or methods of treatment with eculizumab were terminated at Amgen and Alexion's joint request after settlement. The IPRs were instituted in August 2019. Amgen filed Responses in all three on November 22, 2019. Alexion filed its Replies in all three proceedings on February 14, 2020. Amgen filed Sur-replies in all three proceedings on April 27, 2020. Oral Argument was originally scheduled for June 1, 2020, but the joint request for termination was filed on May 29, 2020.

For more information or copies of any of the documents discussed herein, please click here.

Key appellate and district court decisions, new suits, settlements, and other notable events

Litigation Quarterly Update

Key Appellate Developments

Arthrex v. Smith & Nephew. On October 13, 2020, the United States Supreme Court granted certiorari to hear the appeals from the Federal Circuit's decision in *Arthrex Inc. v. Smith & Nephew Inc.*, which found that Patent Trial and Appeal Board administrative judges appointed pursuant to the America Invents Act were principal officers appointed without consent of the Senate in violation of the Constitution's appointments clause, but could still serve as inferior officers by severing certain protections in the Patent Act that increased their independence from the Secretary of Commerce.

AAM v. Becerra. On July 24, 2020, the Ninth Circuit decided the appeal by the Association for Accessible Medicines ("AAM") from the District Court for the Eastern District of California's order denying AAM's motion for a preliminary injunction barring enforcement of California Assembly Bill 824 ("AB 824"). As discussed in more detail in the *featured article* in the last edition of this newsletter, AB 824 was passed to limit the use of so-called "reverse payment" settlements by pharmaceutical companies by establishing a presumption that such payments were anticompetitive if certain conditions were present. The Ninth Circuit found that AAM had neither shown that any of its members faced a "substantial risk" of suffering "injury that is concrete, particularized and imminent" due to enforcement of AB 824, as none of the member companies alleged an intention to engage in reverse payment settlements, nor had they alleged more than "*possible* future injury." Therefore, the Ninth Circuit held that AAM lacked standing to bring claims, and vacated the district court's order denying the motion for preliminary injunction and remanded with instructions to dismiss the claims without prejudice.

Immunex v. Sandoz. On July 31, 2020, Sandoz filed a petition for *en banc* review of the Federal Circuit decision denying Sandoz's appeal from the District Court for the District of New Jersey's determination that Immunex's U.S. Patent No. 8,063,182, claiming the etanercept fusion protein that is the active ingredient in ENBREL®, and U.S. Patent No. 8,163,522, related to the method of manufacturing etanercept, were not invalid for obviousness-type double patenting. As discussed in more detail in the last edition's *Litigation Quarterly Update*, the Federal Circuit panel agreed with the lower court that Immunex had not received "all substantial rights" in the patents-in-suit in its exclusive license from Roche. On September 29, 2020, the Federal Circuit entered an order denying rehearing *en banc* without opinion.

GSK v. Teva. On October 2, 2020, the Federal Circuit entered a decision vacating and remanding the District Court for the District of Delaware's grant of judgment

as a matter of law of no induced infringement in favor of Teva in GlaxoSmithKline's suit accusing Teva's generic carvedilol product of infringing U.S. Patent No. RE40,000 ("the '000 Patent," a reissue of U.S. Patent No. 5,760,069) which claims a method of treating congestive heart failure using carvedilol in conjunction with one or more other therapeutic agents selected from the group consisting of an angiotensin converting enzyme ("ACE") inhibitor, a diuretic, and digoxin. Although this case did not involve a biologic, its holding regarding the limitations of skinny labels could have profound impacts on the biosimilars marketplace. For a more detailed discussion of this case, and its potential impact on biosimilars, please see this edition's featured article.

New Litigation

AAM v. Becerra. On August 25, 2020, the same day that the United States District Court for the Eastern District of California dismissed its previous complaint pursuant to the Ninth Circuit decision discussed above, AAM filed a new complaint against California Attorney General Xavier Becerra challenging the constitutionality of AB 824. As in its previous complaint, AAM alleges that AB 824 violates the Dormant Commerce Clause by regulating conduct and agreements not negotiated or entered into in California, imposes excessive fines prohibited by the Eighth Amendment, and violates AAM's members' due process rights under the Fifth and Fourteenth Amendments. It further alleges that AB 824 is preempted by the Patent Act, the Hatch-Waxman Act, and the BPCIA. AAM attempts to remedy the standing problems that doomed its previous complaint by alleging that AB 824 "has directly compelled AAM members to reject settlement offers and instead continue to spend money litigating cases they otherwise would have settled but for" the law's penalties, and that the law "has also driven some AAM members to withdraw Paragraph IV ANDAs it [*sic*] had previously filed" due to the cost of either litigating or settling and facing potential enforcement of AB 824. The complaint further cites representations made by counsel for Mr. Becerra during oral arguments before the Ninth Circuit to support its Dormant Commerce Clause claims as evidence that the Attorney General "plan[s] to" enforce the law against settlements entered into outside of California. AAM filed a new motion for preliminary injunction on September 14, 2020, and briefing on that motion is ongoing.

Allele v. Regeneron/Pfizer. On October 5, 2020, Allele Biotechnology and Pharmaceuticals, Inc., a biotech company specializing in development of flourescent proteins, filed separate suits in the District Courts for the Southern District of New York and the Southern District of California against Regeneron and Pfizer (along with its partner, German biotech BioNTech SE), respectively. Both suits assert infringement of Allele's U.S. Patent No. 10,221,221 ("the '221 patent"), which claims a non-naturally occurring monomeric flourescent protein known as mNeonGreen. The complaint against Regeneron alleges that the company's monoclonal antibody cocktail was developed using an assay created by encoding the SARS-CoV-2 virus (the novel coronavirus) with the gene sequence for expression of the mNeonGreen protein. The complaint against Pfizer/BioNTech similarly alleges that the companies' mRNA vaccine, currently in phase III trials, was developed using a hybrid SARS-CoV-2/mNeonGreen-based assay. In both suits, Allele is seeking damages, including treble damages for willful infringement of the '221 patent, and attorneys' fees.

Settlements and Stipulations

Genentech v. JHL. On September 9, 2020, Genentech and JHL Biotech, Inc. filed a stipulation in the District Court for the Northern District of California to enter a consent judgment and permanent injunction against JHL. This stipulation was filed pursuant to the settlement agreement reached earlier this summer between the parties resolving Genentech's trade secret misappropriation claims against JHL relating to the alleged theft of Genentech confidential information

by former Genentech employees hired by JHL. The proposed consent judgment and permanent injunction would prohibit JHL and affiliated personnel from using or disclosing any Genentech confidential information, or developing or conducting (or participating in) clinical trials of JHL's biosimilar candidates to Genentech's RITUXAN® (rituximab), AVASTIN® (bevacizumab), HERCEPTIN® (trastuzumab), and PULMOZYME® (dornase alfa) biologics. Rather than immediately entering the proposed consent judgment and permanent injunction, the district court issued an order on September 16, 2020, directing the parties to jointly answer (1) whether the documents submitted to the court comprise the entirety of the agreement between the parties; and (2) why the parties, who remain free to privately settle on agreed terms, want the court to grant an injunction that may contain anticompetitive effects. On September 30, 2020, the parties filed a joint statement affirming that there are no other agreements between them beyond what was submitted to the court, and that the entry of the consent judgment and permanent injunction was a necessary part of the settlement terms between the parties (and provided additional security for Genentech, which could more easily and rapidly petition the court to enforce a violation of the injunction than it could bring a separate breach of contract action for violation of the settlement agreement). The parties further stated that the consent judgment and injunction were actually procompetitive in that they encouraged legitimate competition by punishing unlawful competition via misappropriation of trade secrets. On October 22, 2020, the court entered an order granting the consent judgement and permanent injunction on "the express condition that no party shall cite this order as having immunized this agreement from anticompetitive concerns."

For questions, or copies of any of the decisions or documents discussed herein, please click here.

New biologic and biosimilar launches, legislation, and other marketplace developments

Market Quarterly Update

A new biosimilar launched, legislative proposals to reduce drug costs, and several high-profile large-molecule acquisitions.

Rep. Introduces Proposal to Waive Insulin Interchangeability California Passes Law for State-Sponsored Biosimilars

On September 15, Rep. Glenn Grothman (R-Wis.), introduced a new bill, HR 8190, which – if enacted – would allow approved biosimilar insulins to automatically be granted interchangeability designations to their reference biologic. If passed, HR 8190 would allow for pharmacy-level substitution of cheaper biosimilars for prescribed insulin biologics. The bill is currently pending before the House Energy and Commerce Committee.

California Passes Law Allowing for State-Sponsored Biosimilars and Generics

On September 29, California Governor Gavin Newsom signed into law SB-852, which will create Cal Rx, a state-sponsored label for the manufacture and sale of FDA-approved generic and biosimilar drugs. Under SB-852, the state would enter into partnerships for the manufacture and distribution of such drugs that allegedly would save costs, address market failures, and improve patient access. According to a statement by Gov. Newsom, the state has already begun identifying potential targets; the law requires that California's Health and Human Services Agency identify drugs that could produce the greatest cost savings, and submit a report analyzing how its efforts have impacted competition, access, and costs.

New Insulin Biosimilar Launched

On November 2, 2020, Sanofi announced that it had entered into a definitive agreement to make a public offer to acquire Amsterdam-based Kiadis Pharma, in a deal worth approximately $359 million. Kiadis's pipeline is focused on "off the shelf" natural killer (NK) cell based drugs, with a lead candidate, K-NK002, currently in phase II trials as an adjunct treatment therapy in blood cancer treatment.

On October 26, Bayer announced its acquisition of Asklepios Bipharmaceutical, Inc. (AskBio), a North Carolina-based company focused on AAV gene therapies, in a deal worth $2 billion upfront with up to $2 billion in additional milestone payments. AskBio's

pipeline includes three drugs currently in Phase I/II clinical trials for Pompe disease, Parkinson's disease, and congestive heart failure.

On August 31, Mylan and Biocon Biologics announced the U.S. launch of SEMGLEE™ (insulin glargine injection), a biosimilar to Sanofi's LANTUS® approved for all of the same indications. SEMGLEE™ is available at a WAC of $147.98 per package of five 3 mL pens, or $98.65 per 10 mL vial, a 65% discount over the reference biologic. Mylan and Biocon announced that they were seeking interchangeable designation for SEMGLEE™, which would make it the first approved interchangeable biosimilar in the United States.

Other Market Developments

On August 19, 2020, Johnson & Johnson announced that it had entered into a definitive agreement to acquire Momenta Pharmaceuticals in an all-cash transaction worth approximately $6.5 billion, according to a press release. Momenta's pipeline includes the FcRn antibody nipocalimab, which recently received a rare pediatric disease designation from the FDA, and which recently completed a Phase II clinical trial for generalized myasthenia gravis (gMG).

On September 1, Gilead and Cambridge, Mass.-based Jounce Therapeutics announced a licensing agreement worth $120 million upfront and up to $685 million total for Jounce's preclinical JTX-1811, a monoclonal antibody designed to selectively deplete immunosuppressive tumor-infiltrating T regulatory (TITR) cells. According to a press release announcing the transaction, the antibody is on track for an Investigational New Drug application in the first half of 2021.

On September 4, AbbVie announced that it had entered into a global strategic partnership with Shanghai-based I-Mab Biopharma in a deal worth $180 million upfront with up to $1.74 billion in milestone payments. Under the partnership, AbbVie will exclusively license I-Mab's lemzoparlimab, an anti-CD47 monoclonal antibody that is currently undergoing Phase I studies in patients with relapsed or refractory advanced solid tumors and lymphoma, as a single agent and in combination with Merck's KEYTRUDA or Roche's RITUXAN. An additional $20 million is available based on Phase I results.

For more information or copies of any of the documents discussed herein, please click here.

Key developments at the FDA regarding biologics and biosimilars

FDA/Regulatory Quarterly Update

Recent FDA Biologics and Biosimilar Approvals

FDA Approves TECARTUS™ (brexucabtagene autoleucel)

On July 24, 2020, the FDA approved Kite's TECARTUS™ (brexucabtagene autoleucel), indicated for treatment of adults with relapsed or refractory mantle cell lymphoma. TECARTUS™ is the first CAR T cell therapy approved for mantle cell lymphoma. The FDA granted the application accelerated approval.

FDA Approves MONJUVI™ (tafasitamab-cxix)

On July 31, 2020, the FDA approved MorphoSys's MONJUVI™ (tafasitamab-cxix), indicated for treatment of adults with relapsed or refractory diffuse large B-cell lymphoma. MONJUVI™ was approved by the FDA under accelerated approval. MONJUVI™ is a CD19-directed cytolytic antibody.

FDA Approves BLENREP™ (belantamab mafodotin-blmf)

On August 5, 2020, the FDA approved GlaxoSmithKline's BLENREP™ (belantamab mafodotin-blmf), indicated for treatment of adults with relapsed or refractory multiple myeloma who have received at least four prior therapies. BLENREP™ is a B-cell maturation antigen directed antibody and microtubule inhibitor conjugate. The FDA granted the application accelerated approval.

FDA Approves ENSPRYNG™ (satralizumab-mwge)

On August 14, 2020, the FDA approved Genentech's ENSPRYNG™ (satralizumab-mwge), indicated for treatment of neuromyelitis optica spectrum disorder in adults who are anti-quaporin-4 antibody positive. The FDA granted the application Orphan Drug designation.

FDA Approves SOGROYA™ (somapacitan-beco)

On August 28, 2020, the FDA approved Novo Nordisk's SOGROYA™ (somapacitan-beco), indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency. SOGROYA™ is the first

human growth hormone therapy that patients take only once a week by injection.

FDA Approves NUCALA™ (mepolizumab)

On September 25, 2020, the FDA approved GlaxoSmithKline's new indication of NUCALA™ (mepolizumab), for treatment of patients with hypereosinophilic syndrome ("HES") for six months or longer without another identifiable non-blood-related cause of the disease. NUCALA™ is the first approval for HES patients in almost 14 years. The FDA granted the application Orphan Drug designation, fast track designation, and priority review.

For more information or copies of any of the documents discussed herein, please click here.

Recent Developments in Antitrust Law

The Federal Circuit Finds Induced Infringement Despite the Use of a Skinny Label

The Federal Circuit decision in *GlaxoSmithKline, LLC v. Teva Pharmaceuticals USA*, Inc. has potential implications for the use of skinny labels in both the small molecule and biosimilar context. This article discusses the *GSK v. Teva* litigation and how this decision may impact the future use of skinny labels for biosimilars.

Skinny Labels Under the Hatch-Waxman Act and the BPCIA

A "skinny label" refers to the practice of follow-on drug manufacturers seeking approval for some but not all of the indications for which the reference drug product has been approved. Under the Hatch-Waxman Act, a filer of an abbreviated new drug application (ANDA) may seek approval of less than all reference product indications by submitting a statement under Section 505(j)(2)(A)(viii), known as a "Section viii statement." Section viii carve-outs are permissible if information relating to the patented use can be removed from the label without sacrificing safety and efficacy. The resulting skinny label will copy only the portions of the reference product label that correspond to the selected indications. This is meant to ensure that subsequent method of treatment patents do not prevent the launch of generic drugs for unpatented uses. However, in the small molecule context, AB-rated generics are routinely and automatically substituted for the reference product, even for uses that have been carved out under Section viii.

For biosimilars, there is no equivalent to a Section viii carve-out in the BPCIA. Nevertheless, FDA guidance makes clear that an applicant "may decide not to seek licensure of a proposed biosimilar or proposed interchangeable product for conditions of use that are protected by patent, according to the applicant's own assessment." *See* FDA Draft Guidance at 4, *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed* (Feb. 2020). Notably, however, Section 351(k)(4)(A) of the Public Health Service Act provides, among other things, that an application for an interchangeable product must include information sufficient to show that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient." As such, the FDA has stated that applicants seeking to demonstrate interchangeability must submit data and information to support a showing that the proposed interchangeable product can be expected to produce

the same clinical result as the reference product in *all* of the reference product's licensed conditions of use. *See Guidance for Industry Considerations in Demonstrating Interchangeability with a Reference Product* (May 2019).

In a recent decision, the Federal Circuit dealt with these issues as they relate to small-molecule drugs and reinstated a jury verdict that found a generic product with a skinny label willfully infringed a carved-out method of treatment patent based on its label and marketing materials. The decision has potentially broader implications for skinny labels and the law with respect to induced infringement.

The District Court Proceedings and Decision

In May 1997, the FDA approved carvedilol as the first beta-blocker for the treatment of congestive heart failure ("CHF"), leading to GSK's launch of Coreg®, the brand name of its carvedilol tablets. GSK received U.S. Patent No. 5,760,069 (the "'069 patent"), which is directed toward methods of decreasing CHF mortality by administering carvedilol in conjunction with an ACE inhibitor, a diuretic, or digoxin. On January 8, 2008, the '069 patent reissued as RE40,000 (the "'000 patent"). The '000 patent expired on June 7, 2015.

In March of 2002, Teva filed an ANDA to market generic carvedilol tablets. Teva submitted a paragraph IV certification asserting that the '069 patent was invalid, but submitted a paragraph II certification with respect to a carvedilol composition patent that expired in March 2007. In August 2007, Teva sought to carve out the CHF indication covered by the '069 patent from its generic label. On September 5, 2007, Teva received FDA approval and launched its generic tablets with the skinny label. In April 2011, Teva amended its label to be a complete copy of GSK's full label after receiving a letter from the FDA stating that GSK had delisted the '069 patent. From January 2008 to April 2011, Teva sold generic carvedilol under a skinny label that did not include the method of using carvedilol for the treatment of mild to severe CHF as recited in the '000 patent. After April 2011, Teva sold its generic under a full label. In 2014, GSK sued Teva for induced infringement of the '000 patent.

In a seven-day jury trial in the District of Delaware, Teva argued that since it had carved out from its initial label the indication and prescribing information for treatment of CHF, Teva could not be found to induce prescribing physicians to infringe the '000 patent, at least not before Teva amended its label to include all indications in 2011. GSK relied on Teva's marketing materials—Teva's 2008 and 2009 product catalogs and Teva's 2009 Generic Product Reference Guide—that allegedly trumpeted Teva's AB rating without expressly stating that Teva's generic carvedilol was not approved for treatment of CHF. GSK argued that this marketing of the AB rating without a disclaimer that Teva's generic carvedilol was not approved to treat CHF induced infringement of the '000 patent. The jury returned a verdict of willful induced infringement during both the skinny label period and the full label period and found no invalidity of the '000 patent. The jury awarded $234,110,000 in lost profits and $1,400,000 in reasonable royalty damages. The district court subsequently granted JMOL in favor of Teva, finding that "substantial evidence does not support the jury's findings on inducement in either the skinny or full label period."

With respect to the skinny label period, the district court found that a reasonable jury could only find that any direct infringement by physicians was caused by factors unrelated to Teva. GSK presented no direct evidence that Teva's label (whether skinny or full) caused even a single doctor to prescribe generic carvedilol to treat CHF. Rather, GSK relied on indirect evidence, including Teva's AB rating as well as marketing materials that did not expressly disclaim using Teva's product for treatment of CHF to show inducement. In the district court's view, however, this evidence could not support a reasonable finding that Teva caused any infringement of GSK's '000 patent because (1) there is no FDA requirement that a generic drug company specify for which uses it is (or is

not) AB rated, (2) neither party's experts had ever seen such a clarifying statement in any press release or product catalog, (3) the Orange Book states that therapeutic equivalent determinations are not made for unapproved off-label indications, and (4) GSK's expert admitted that AB rating is limited to the use of the drug in accordance with its own label. In addition, the district court cited evidence that when generic companies (including Teva) began selling carvedilol, doctors relied on guidelines and research, as well as their own experience, in addition to GSK marketing rather than on the generic label to make prescribing decisions. Based on this, the district court found that there was insufficient evidence to support a finding that Teva induced infringement during the skinny label period.

With respect to the full label period, the district court again found that a reasonable factfinder could only have concluded that alternative, non-Teva factors were what caused doctors to prescribe generic carvedilol for the treatment of CHF. The district court noted that no substantial evidence was presented at trial to support a finding that anything about the behavior of doctors —as a class, or even a single doctor — was induced to change by the modification of Teva's label, or by anything else Teva did (or failed to do). For all these reasons, the district court found that a reasonable jury could not find that Teva had caused any direct infringement and, therefore, Teva could not be held liable for inducement of infringement.

GSK appealed.

The Federal Circuit Decision

On appeal, GSK argued that Teva's marketing of carvedilol with knowledge and intent of its infringing use, and promotion of its generic product as the same as Coreg®, met the legal requirements of active inducement of infringement. GSK further argued that the district court erred as a matter of law because induced infringement may be shown by evidence that the accused inducer promoted the infringing use with knowledge that such use directly infringes the patent claims. Teva countered that it could not be liable for inducing infringement because cardiologists already knew of carvedilol and its uses, and Teva did not directly "cause" them to infringe.

On October 2, 2020, the Federal Circuit reversed the JMOL in a 2-1 decision. Judge Newman wrote the majority opinion, joined by Judge Moore. Judge Prost wrote a dissenting opinion agreeing with the district court.

Citing the Supreme Court decisions in *Global-Tech Appliances, Inc. v. SEB S.A.* and *MGM Studios Inc. v. Grokster, Ltd.*, the majority explained that the copying of a patented product is evidence of inducing infringement and such inducement is not negated when the direct infringers already knew of the infringing subject matter. The majority then analyzed the evidence that was before the jury, including Teva's promotional materials, which referred to Teva's carvedilol tablets as AB-rated equivalents of the Coreg® tablets. In addition, the majority focused on the testimony of GSK's expert, Dr. McCullough, who testified that doctors are "completely reliant" on information provided by generic producers, and that doctors receive Teva's product catalogs, visit its website, and read its product guides.

Teva argued that it could not be liable for induced infringement because it had deliberately carved out from its 2007 label reference to congestive heart failure. The majority rejected Teva's argument, however, pointing to testimony from Teva's 30(b)(6) witness that carving out a particular indication was a legal strategy, not a commercial strategy, and that Teva expected to receive sales when a doctor prescribed carvedilol for CHF. Dr. McCullough also testified that the 2007 Press Release that announced final approval of Teva's generic version of Coreg® "indicates that we should be able to prescribe generic carvedilol for heart failure." The majority also credited GSK's expert witness on the regulatory process, who explained that the FDA's "general position is that if

you compare one product to another by name, you are implying the use of the product."

The majority found that this evidence was legally sufficient to support the jury verdict because "when the provider of an identical product knows of and markets the same product for intended direct infringing activity, the criteria of induced infringement are met."

The majority reversed the district court's grant of JMOL, and remanded for entry of judgment on the verdict.

The Dissent

The dissent argued that by marketing its generic carvedilol for unpatented uses through a skinny label, Teva could not be found liable for inducing infringement of the '000 patent.

The dissent first addressed the statutory background, emphasizing that skinny labels were designed by Congress to ensure that "one patented use would not foreclose a generic from marketing a drug for other unpatented uses." The dissent argued that Teva had acted as Congress intended: Teva waited until GSK's patent covering the carvedilol compound expired to launch its product covering two unpatented indications—hypertension and post-MI LVD. Moreover, when the '000 patent issued covering the treatment of CHF, Teva's skinny label did not suggest using its product according to the patented method. Agreeing with the district court, the dissent also noted:

> [N]o evidence established that Teva actually caused the doctors' infringement for either label. No communication from Teva encouraged doctors to use generic carvedilol to practice the patented method. And no evidence showed that doctors relied on Teva's label. Indeed, GSK's own expert admitted that he had not read Teva's label before prescribing generic carvedilol. Rather than suggest inducement, the record established that doctors relied on other sources of information, not Teva, in making their decision to prescribe carvedilol. And in any case, the record showed that the switch from Coreg® to generic carvedilol occurred "automatically," often without doctors' knowledge at all.

The dissent further criticized the majority opinion as finding that "the 'content' of Teva's skinny label alone is sufficient to prove induced infringement—even though Teva's skinny label did not encourage, promote, recommend, or even suggest the patented method." Contrary to the majority opinion, the dissent also found that the additional marketing materials failed to provide substantial evidence of inducement because the documents did not encourage the patented use and the doctors relied on other sources, not Teva's documents, in prescribing carvedilol.

The dissent concluded that "this result discourages generics from entering the market in the first instance" because "it was ultimately more costly for Teva to sell an unpatented drug for unpatented uses than it would have been to stay out of the market altogether."

Potential Impact on Biosimilars

Although *GSK v. Teva* is specific to generic products under the Hatch-Waxman Act, this decision gives rise to potential implications with respect to label carve-outs for biosimilars. As noted at the beginning of this article, it is also possible to carve out indications for biosimilars. Indeed, this is a common approach for biosimilar products, as is shown in the table following this article.

In the generic context, this decision suggests that creating an uncorrected impression of equivalence may be sufficient to prove inducement, even for a carved-out indication. But there are important differences between biosimilars and small molecule generics that could potentially lead to a different result than that of *GSK v. Teva*. Most notably, biosimilars are not AB rated

but instead are found to be "biosimilar" to the reference product. However, proving biosimilarity requires establishing that the two products are "highly similar"; it does not require that the products be exactly the same. Thus, advertising that a product is "biosimilar" to a reference product may not carry the same weight as advertising a product as an AB-rated generic.

In addition, the majority cited the fact that Teva expected to receive sales based on the carved-out indication. However, unlike AB-rated generics, biosimilars are not automatically substituted for branded products by pharmacies. Although there is a pathway to earn an "interchangeable" designation, no biosimilar has received that designation to date. As a result, carving out an indication for a biosimilar may mean that it will not have sales related to that indication.

Additionally, the parties in the Teva case disputed to what extent physicians reviewed and relied upon both the labels and the marketing materials provided by Teva. In the biosimilar context, physicians may potentially be more likely to review the materials and the label before using a biosimilar, possibly decreasing the likelihood of an inducement finding. Furthermore, biosimilar manufacturers may market their products more than a generic product, and these additional marketing materials may support an argument that a biosimilar was advertised for only the uses set forth on its own label.

However, there is still a risk that marketing a biosimilar by comparing it to the reference product or describing biosimilarity in broad terms as equivalent to the reference product could be considered circumstantial evidence of infringing a carved-out method of treatment patent. Biosimilar applicants pursuing a skinny label should carefully scrutinize marketing materials for any implication that the biosimilar could be prescribed for all indications of the reference product.

Teva has stated that it will appeal the decision and may seek *en banc* review by the full Federal Circuit. Under Federal Circuit Rules, Teva has thirty days (until November 2) to petition for rehearing *en banc*.

For more information or copies of any of the documents discussed herein, please click here.

BIOSIMILAR	REFERENCE PRODUCT	PUBLICLY REPORTED CARVED-OUT INDICATIONS
Zarxio	Neupogen (filgrastim)	Hematopoietic Syndrome of Acute Radiation Syndrome[1]
Nivestym	Neupogen (filgrastim)	Hematopoietic Syndrome of Acute Radiation Syndrome
Fulphila	Neulasta (pegfilgrastim)	Hematopoietic Sub-syndrome of Acute Radiation Syndrome
Udenyca	Neulasta (pegfilgrastim)	Hematopoietic Sub-syndrome of Acute Radiation Syndrome
Ziextenzo	Neluasta (pegfilgrastim)	Hematopoietic Subsyndrome of Acute Radiation Syndrome
Nyvepria	Neulasta (pegfilgrastim)	Hematopoietic Subsyndrome of Acute Radiation Syndrome
Inflectra	Remicade (infliximab)	Pediatric Ulcerative Colitis
Renflexis	Remicade (infliximab)	Pediatric Ulcerative Colitis
Ixifi	Remicade (infliximab)	Pediatric Ulcerative Colitis
Avsola	Remicade (infliximab)	--
Erelzi	Enbrel (etanercept)	Psoriatic Arthritis Plaque Psoriasis in patients 4 years or older
Eticovo	Enbrel (etanercept)	--
Hyrimoz	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis
Amjevita	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis
Hadlima	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis
Hulio	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis

[1] Note: This indication was added to the Neupogen label March 30, 2015, after Zarxio was approved on March 6, 2015.

BIOSIMILAR	REFERENCE PRODUCT	PUBLICLY REPORTED CARVED-OUT INDICATIONS
Abrilada	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis
Cyltezo	Humira (adalimumab)	Pediatric Crohn's Disease Hidradenitis Suppurativa Uveitis
Mvasi	Avastin (bevacizumab)	Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer[2]
Zirabev	Avastin (bevacizumab)	Epithelial ovarian, fallopian tube, or primary peritoneal cancer Hepatocellular Carcinoma (HCC)
Ogivri	Herceptin (trastuzumab)	--
Herzuma	Herceptin (trastuzumab)	The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
Ontruzant	Herceptin (trastuzumab)	--
Kanjinti	Herceptin (trastuzumab)	--
Trazimera	Herceptin (trastuzumab)	--
Retacrit	Epogen/Procrit (epoetin alfa)	--
Truxima	Rituxan (rituximab)	Non-Hodgkin's Lymphoma (NHL) with Previously untreated diffuse large B-cell, CD20-positive NHL Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangitis and Microscopic Polyangitis Pemphigus Vulgaris
Ruxience	Rituxan (rituximab)	Rheumatoid Arthritis Pemphigus Vulgaris

[2] Note: This comparison is based on the 2016 Avastin label. The 2018 Avastin label removed many of the previously approved indications, such that Mvasi listed more indications than Avastin.

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